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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPIVACK, PHYLLIS G	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,022	LUKAS-LASKEY ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicants' Reply filed April 2, 2007 is acknowledged. Claims 1-30 remain under consideration.

Declarations filed by Neil H. Shusterman, M.D. and Martin Wehling, M.D., as well as an Affidavit of Dr. Mary Ann Lukas and a copy of *Rappoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), are further acknowledged and have been considered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 14, 15, 17, 18, 22, 23 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. See *In re Rasmussen*, 211 USPQ 323. The recitation in claims 1, 14, 17, 22, 26 and 27 "maintenance period is greater than six months" is new matter. The recitation "to statistically decrease the risk of mortality caused by congestive heart failure" in claims 12, 15, 18, 23 and 28 is new matter.

Various trials are discussed in column 7 in U.S. Patent 5,902,821. On lines 56-58 the maintenance phase of each study is stated to range from six to 12 months. The referenced protocols do not correlate with the recited limitations in each of the present claims with respect to a "maintenance period."

The specification fails to provide statistical support for each of the claimed methods with respect to dosages and dosing regimens.

In the last Office Action claim 9 was rejected under 35 U.S.C. 102(a) as being anticipated by Metra et al. Journal of the American College of Cardiology. It was asserted Metra teaches the oral administration of 6.25 mg of carvedilol twice a day for 7 days. See the Abstract under *Methods*. Metra teaches the addition of carvedilol to "standard therapy", which meets the limitation of claim 9 drawn to "in combination with at least one other therapeutic agent". The open language of claim 9, i.e., the recitation of "comprising," allows for the inclusion of additional therapeutic options.

Additionally, claims 1-8 and 10-30 were rejected in the last Office Action under 35 U.S.C. 103(a) as being unpatentable over Olsen et al., Journal of the American College of Cardiology, and Metra et al., in view of Journal of the American College of Cardiology. It was asserted Olsen teaches the oral administration of an initial dose of 3.125 mg of carvedilol twice daily for one week to improve both symptoms of congestive heart failure and left ventricular function in patients with congestive heart failure. In a second phase of administration, 6.25 mg of carvedilol is given twice daily and titrated over one month to a maximum dose of 25 mg twice daily for those patients weighing less than 75 kg and 50 mg twice daily for those patients weighing over 75 kg. In a third phase of administration, the dosing continued for three additional months. Accordingly, Olsen's teaching meets or suggests the dosing regimen requirements of claims 1, 7, 10, 20 and 26 with respect to the length of time of administration, the

amount of drug given to patients and the daily administration requirements in each part of the triphasic claimed protocols. Metra provides a clear teaching drawn to a reduction in a risk of mortality in patients suffering from congestive heart failure. See the Abstract under *Conclusions* where Metra teaches the administration of carvedilol to both reduce heart rate and mean pulmonary artery and pulmonary wedge pressures in the short-term, and, improve exercise left ventricular systolic function and reduce heart failure symptoms in the long-term. In patients with idiopathic cardiomyopathy, administration of carvedilol improves submaximal exercise tolerance.

Applicants have responded to both rejections set forth in the last Office Action together.

Applicants argue a treatment for congestive heart failure symptoms is distinct from treatment to decrease a risk of CHF mortality. Applicants urge beta blockers were contraindicated for the treatment of CHF patients. In particular, Applicants cite *Rapoport* wherein the Federal Circuit interpreted treatment of sleep apneas to refer to sleep apnea treatment *per se*, not treatment of symptoms associated with sleep apnea. Further, according to Dr. Lukas, symptomatic improvement does not predict the effect of the treatment on mortality. Dr. Shusterman declares a mortality reduction of about 67% was found for class II-IV CHF patients.

Applicants' arguments have been given careful consideration but are not found persuasive. The rejection of record of claim 9 under 35 U.S.C. 102(a) is maintained for the reasons reiterated below.

Claim 9 is drawn to a method of treating to decrease a risk of mortality, comprising administering carvedilol once or twice daily, alone or in combination with at least one other therapeutic agent for a period of 7 to 28 days. See the Abstract under *Conclusions* where Metra teaches the administration of carvedilol to both reduce heart rate and also mean pulmonary artery and pulmonary wedge pressures in the short-term, and, improve exercise left ventricular systolic function and reduce heart failure symptoms in the long-term. In patients with idiopathic cardiomyopathy, administration of carvedilol improves submaximal exercise tolerance. Accordingly, carvedilol clearly decreases a risk of mortality in patients who suffer from the inability of the heart to maintain adequate blood circulation in the peripheral tissues and the lungs, and in patients having the clinical syndrome that defines congestive heart failure, i.e., shortness of breath, pitting edema, enlarged tender liver, engorged neck veins and pulmonary rales.

The rejection of claims 1, 2, 7, 10, 11, 20, 21, 26 and 30 under 35 U.S.C. 103 is maintained for the reasons reiterated below. The rejection of claims 3-6, 8, 9, 12-19, 22-25 and 27-29 is withdrawn.

In view of the combined teachings of Olsen and Metra, one skilled in the cardiology art would have been motivated to administer carvedilol in a treatment regimen that comprises a first dosage (3.125 mg or 6.25 mg or 10-30% of the daily maintenance dosage) at least daily for a period of 7 days, followed by a second dosage (12.5 mg or 20-70% of the daily maintenance dosage) for a period of 7 days to a month and finally a third dosage (10-100mg carvedilol) for a maintenance period. The actual determination of an optimal

duration and dosage of each phase of therapy and, in particular, the maintenance phase, would reasonably be determined by the skilled practitioner in cardiology, in view of each individual patient's medical profile, through no more than routine experimentation, and, in particular, in view of the guidelines provided by the prior art.

The instantly claimed method of decreasing a risk of mortality through administration of carvedilol would have been *prima facie* obvious at the time of the invention. The skilled artisan would have been highly motivated to administer carvedilol because it reduces heart failure symptoms and improves long-term rest and exercise left ventricular systolic function. Further, the prior art teaches advantages between carvedilol and other beta blockers. Carvedilol exhibits both beta-adrenergic blocking and precapillary vasodilating activity. Other beta blockers do not exhibit such dual functionality. Another distinction of carvedilol administration is its very low adverse effect profile when compared to other beta blockers. The skilled artisan would have been imbued with at least a reasonable expectation that carvedilol would be an effective treatment to decrease the risk of mortality in patients having congestive heart failure. Reducing the risk of mortality is broadly interpreted as meaning not only a decrease in the death rate, but also the qualities and conditions of being liable or subject to death. Accordingly, the teachings of Metra provide a reasonable expectation of success in decreasing a risk of mortality caused by congestive heart failure through administration of carvedilol.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen et al., Journal of the American College of Cardiology, and Metra et al., Journal of the American College of Cardiology, in view of The Merck Index, and Schnurr et al., Journal of Cardiovascular Pharmacology.

Olsen teaches the oral administration of an initial dose of 3.125 mg of carvedilol twice daily for one week to improve both symptoms of congestive heart failure and left ventricular function in patients with congestive heart failure. In a second phase of administration, 6.25 mg of carvedilol is given twice daily and titrated over one month to a maximum dose of 25 mg twice daily for those

patients weighing less than 75 kg and 50 mg twice daily for those patients weighing over 75 kg. In a third phase of administration, the dosing continued for three additional months. Accordingly, Olsen's teaching meets or suggests the dosing regimen requirements of claims 1, 7, 10, 20 and 26 with respect to the length of time of administration, the amount of drug given to patients and the daily administration requirements in each part of the triphasic claimed protocols. Metra provides a clear teaching drawn to a reduction in a risk of mortality in patients suffering from congestive heart failure because reducing the risk of mortality is broadly interpreted as meaning not only a decrease in the death rate, but also the qualities and conditions of being liable or subject to death. See the Abstract under *Conclusions* where Metra teaches the administration of carvedilol to both reduce heart rate and mean pulmonary artery and pulmonary wedge pressures in the short-term, and, improve exercise left ventricular systolic function and reduce heart failure symptoms in the long-term. In patients with idiopathic cardiomyopathy, administration of carvedilol improves submaximal exercise tolerance. In view of efficacy in treating the parameters that are part of the definitions of the NYHA classification, the teachings of Mehta encompass those patients having class II-IV congestive heart failure. These patients would reasonably be characterized as having cardiac disease resulting in either slight/moderate or marked limitations of physical activity or an inability to carry on any physical activity without discomfort. Neither Olsen or Metra teach dosage administration during maintenance period beyond 4 months, nor the

administration of "other therapeutic agents," as required by instant claims 3-6, 8, 14, 15, 17, 18, 22, 23 and 25-29.

However, The Merck Index teaches the administration of conventional pharmaceutical drugs for CHF patients. Angiotensin converting enzyme inhibitors (page 1689), diuretics (page 1688) and cardiac glycosides (pages 1689-1690) are required medicaments.

Schnurr teaches the maintenance administration of carvedilol for a period of one year with no serious side effects.

Therefore, in view of the combined teachings of the prior art, a skilled cardiologist would have been motivated to administer carvedilol to treat congestive heart failure in a tiered dosing regimen with respect to dosages and length of therapy with a reasonable expectation of success in reducing the risk of mortality through no more than routine experimentation.

With respect to claimed dosing regimens of carvedilol in the instant methods of use, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(II). The determination of the optimum dosage regimen to employ with the presently claimed active agent would have been a matter well within the purview of one of ordinary skill in the art. Such determination would have been made in accordance with a variety of factors. These would have included such factors as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological

considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered a part of a drug combination. Thus, in the absence of evidence to the contrary, the currently claimed specific dosage amounts and dosage regimens are not seen to be inconsistent with the dosages that would have been determined by the skilled artisan.

Reducing the risk of mortality relates to the qualities and conditions of being liable or subject to death, as well as death rate.

No claim is allowed.

Stedman's Medical Dictionary is cited to provide definitions of "mortality." Eggertsen et al., Eur. Journal Clin. Pharmaocology, is cited to show further the state of the art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel can be reached on 591-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack

May 10, 2007

Phyllis G. Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER